REMARKS/ARGUMENTS

**Interview Summary**

Applicants' counsel wishes to thank Examiners Ardin Marschel and Michel Graffeo for participating in a telephone interview with Applicants' counsel on June 29, 2007. Although no agreement was reached as to allowable subject matter at that time, Applicants' counsel gained a greater appreciation for the position of the Examiners. During the interview, Applicants' counsel explained the differences between the claimed invention and the art cited in the non-final Office Action mailed March 23, 2007.

During the interview, Applicants' counsel pointed out that the cited Scaife patent (US 6,407,128) is directed to a method using commercial Skelaxin® with food, and that while the extent of absorption is increased when commercial Skelaxin® is administered to a patient with food, the rate of absorption (as evidenced by Tmax in Table IIb in Col. 5 of Scaife) is actually less than when administered to a patient without food. During the interview, Applicants' counsel noted that claim 1 of the present application claims a composition that increases both the extent of absorption (AUC number) and the rate of absorption (Tmax number) when administered to a patient on an empty stomach over that of commercial Skelaxin® as disclosed in Scaife, and that these features are demonstrated in Table 8 of the present application. It was also noted during the interview that commercial Skelaxin®, identified as the composition in Scaife, is the same as the composition identified in New Drug Application No. 13-217, as confirmed by the Orange Book listing.

**Amendment to the Specification**

The specification has been amended to clarify the teaching of the Scaife reference. No new subject matter has been added to the specification.

**Rejections under 35 USC 112, first paragraph**

In the non-final Office Action mailed March 23, 2007 claims 1, 3-18, and 23 were rejected under 35 U.S.C. 112, first paragraph for failing to comply with the written description



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requirement. It is respectfully submitted that the amendment to claim 1 renders the Section 112 rejection to the pending claims moot.

Claim 1 now claims "A pharmaceutical composition comprising metaxalone in a pharmaceutically acceptable solubility-improved form and at least one pharmaceutically acceptable excipient, characterized in that the pharmaceutical composition has enhanced oral bioavailability as compared to the pharmaceutical composition of metaxalone described in New Drug Application No. 13-217 when they are administered to a patient on an empty stomach."

The Office Action indicated that the above language would render the Section 112 rejection moot.

**Rejections under 35 USC 103(a)**

Claims 1, 3-15 and 27 were rejected as being unpatentable over Scaife et al. U.S. Patent No. 6,407,128 in view of Gilis et al. U.S. Patent No. 6,030,988. Claims 16-18 were rejected as unpatentable over Scaife et al. as applied to claims 1, 3-15 and 27 above in view of Cheng et al. U.S. Patent No. 6,099,859. Claim 23 was rejected as unpatentable over Scaife et al. as applied to claims 1, 3-15, and 27 above. These rejections are respectfully traversed.

The Office Action concedes that Scaife et al. does not teach any particular values for the size of metaxalone particles in the dosage form nor name any particular solubilizing agent. It is undisputed that Scaife does not suggest any other form of metaxalone other than the conventional form described in the New Drug Application No. 13-217. The Office Action also does not dispute that Scaife discloses that providing metaxalone in conventional form with food is a satisfactory solution to Scaife's concerns with bioavailability.

One of ordinary skill in the art, having the benefit of Scaife's "food" solution, would not be motivated to deviate from Scaife. Scaife says nothing about using a form of metaxalone that is different from that described in NDA 13-217. It is respectfully submitted that by only teaching one approach (evaluating the effect of food on the pharmacokinetics of the conventional form of metaxalone) and only teaching one solution (administering the conventional form of



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metaxalone to a patient with food), Scaife does in fact teach away from an approach to increase oral bioavailability of metaxalone by administering it to a patient on an empty stomach.

It is further noted that Table II b Column 5 of Scaife states that the Scaife composition when administered to a patient without food has a faster Tmax (Time to reach the peak plasma level of 3.32 hours) and lower AUC numbers than the same composition when administered to a patient with food (Tmax time is 4.29 hours). Thus, Scaife teaches that while the AUC numbers are greater (i.e., extent of absorption) when the Scaife composition is given to a patient with food than without food, it takes longer to reach peak levels (i.e., rate of absorption) when the Scaife composition is given to a patient with food than without food.

Although Scaife (in column 6, lines 36-37 and lines 45-47) concludes that the composition has a higher rate and extent of absorption, such conclusion is incorrect in view of an increase in Tmax upon administration with food. Tmax is a parameter closely related to the rate of absorption and may be used as a simple measure of rate of absorption. (See Remington's Pharmaceutical Sciences", 18th Edition, Mack Publishing Company, Easton, Pennsylvania, 1990, page 1455, Exhibit A).

Generally, Tmax is related to the rate constant of absorption $k_a$ by the equation:

$$Tmax = \frac{2.303}{k_a - K} \log \frac{k_a}{K}$$

K is the rate constant of elimination of drug from the body, and is unaffected by the presence of food. Therefore, changes in Tmax are related to changes in apparent rate constant of absorption.

On the other hand Cmax is given by the equation:

$$Cmax = \frac{F X_0 e^{-KTmax}}{V}$$

where F is the extent of absorption, $X_0$ is the dose, V is the volume of distribution, and Tmax the time to peak plasma concentration. (See Milo Gibaldi et al., pg 37-38, Equations 1.106 and 1.110, Exhibit B).



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Therefore, Cmax is dependent on both extent (F) and rate of absorption, i.e., Tmax. An increase in Cmax without a decrease in Tmax may thus be only due to an increase in the extent of absorption, i.e., F. For further background generally regarding the rate and extent of absorption, see Bioavailability and Bioequivalence: General Concepts and Overview, by Prof Richard Bergstrom et al. of Indiana University, posted on the net at: http://medicine.iupui.edu/clinical/F813_spring2006/Q_ClinicalPKF813Lecture16A07March2006BioavailabilityandBioequivalencerevised.pdf, a copy of which is attached as Exhibit C.

On the other hand, Table 8 of the present application shows both a decrease in Tmax (i.e., rate of absorption) and an increase AUC numbers (i.e., extent of absorption) over the Skelaxin composition (i.e., the Scaife composition) when those compositions are administered to patients without food. This is unexpected in view of the teachings of Scaife that increasing the extent of absorption comes by administering the Scaife composition with food also results in an increase in Tmax, i.e., a decrease in the rate of absorption.

Whereas administration of the Scaife composition with food leads to longer time to attain peak plasma level, the present invention does the opposite – *i.e.*, it takes less time to reach the peak plasma level in the present invention. Please note that at the specification of the present invention (as published as US 2006/0167069) on page 3, the last sentence of para [021] makes clear that the biovailability referred to in the present application is both the rate and extent of absorption.

It is respectfully submitted that the Office Action does not establish a *prima facie* case of obviousness. At the time of the present invention, there was no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify Scaife, or to combine Scaife with Gilis or Cheng. In addition, at the time of the present invention, there was no reasonable expectation of success in modifying Scaife or combining Scaife with Gilis or Cheng. Indeed, the Office Action does not contend that there was a reasonable expectation of success at the time of the present invention.

The Office Action states that "the burden is on the Applicant to show that the bioavailability of the obvious formulation (that taught in the combination of references) is



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greater than that described in the NDA." First, Applicants disagree that there the claimed invention is an "obvious" formulation. Second, Applicants have shown by way of comparison testing that the claimed invention has better bioavailability than the conventional form described in the NDA.

The Office Action argues that it would be obvious to modify Scaife in view of Gilis and Cheng because Scaife cites Gilis and Cheng. The Office Action does not cite to any legal support for such rigidity. The U.S. Supreme Court recently rejected "a rigid application" in the context of an obvious/non-obvious determination. *See* Memorandum of May 3, 2007, from Margaret A. Focarino, Deputy Commissioner for Patent Operations regarding the Supreme Court decision on *KSR Int'l Co. v. Teleflex, Inc.* "[I]t remains necessary to identify the reason why a person of ordinary skill would have combined the prior art elements in the manner claimed." *Id.* Stating that "one reference is cited by another" is not a reason why a person of ordinary skill would have combined prior art elements. For example, that one reference takes one approach, and cites to a reference that takes a different approach to solve the same or different problem is an indication that the one of ordinary skill in the art would not be motivated to combine prior art elements in the references.

The proposed modification cannot change the principle of operation of a reference. MPEP 2143.01 (VI), citing *In re Ratti*, 270 F.2d 810, 813 (C.C.P.A. 1959). In *Ratti*, the court reversed the rejection holding the "suggested combination of references would require substantial reconstruction and design of the elements shown in [the primary reference] as well as change the basic principle under which the [primary reference] construction was designed to operate." [Emphasis added]. Here, the Office Action proposes to modify the primary reference Scaife that would change the basic principle under which Scaife was designed to operate, i.e., "with food."

When the four factors in *Graham v. John Deere* are correctly applied in this case, it is apparent that the claimed invention is non-obvious over the cited art. Scaife teaches that the conventional form of metaxalone has lower extent of absorption and higher rate of absorption when administered without food than with food, and teaches no other way to increase extent of



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absorption than administering its composition with food – which results in a decrease in the rate of absorption.

Gilis does not mention a pharmaceutical composition comprising metaxalone. The Office Action contends, however, that Gilis teaches that a micronized formulation of any drug results in enhanced bioavailability. This contention is incorrect.

Bioavailability as referred to in the specification in the present application means both the rate and extent to which the active ingredient is absorbed into the systemic circulation from the pharmaceutical composition. *See* the present application as originally filed at page 1, lines 6-10, page 2, lines 8-10, page 2, lines 20-23, page 6, lines 5-7.

However, whether it is in fact possible to obtain such an enhancement of both rate and extent of absorption of a particular drug cannot be predicted. In other words, if for example one micronized drug shows improved bioavailability, it does not naturally extend or be extrapolated to metaxalone.

For example, "Remington's Pharmaceutical Sciences", 18th Edition, Mack Publishing Company, Easton, Pennsylvania, 1990, page 1437 (a copy of which was submitted in a Supplemental Information Disclosure Statement on October 13, 2006) it is stated that "For chloramphenicol, particle size has virtually no effect on total absorption but it significantly affects the rate of appearance of peak blood levels of the drug." On the other hand, the paragraph above this paragraph this sentence recites the example of sulfadiazine which showed an increase in both the rate and extent of absorption. This therefore demonstrates that it is unpredictable whether both rate and extent of absorption will be enhanced by decreasing particle size.

Therefore, different results are obtained with different drugs and it would not be obvious to a person of ordinary skill in the art to reduce the particle size of metaxalone with a reasonable expectation of success that both rate and extent of absorption of metaxalone will be improved when given on an empty stomach.

A person of skill in the art is aware that reduction in particle size can have undesirable effect on drugs. See "Remington's Pharmaceutical Sciences", 18th Edition, Mack Publishing Company, Easton, Pennsylvania, 1990, pp 1437 which recites as below:



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> Particle-size reduction may be deleterious for some drug substances. Increasing surface area by milling or other methods may lead to rapid degradation of a compound. Drug substances also may undergo polymorphic transformation during the milling process.
>
> ***
>
> Reduction of particle size also may create adverse responses. For example, fine particles of the prodrug trichloroethyl carbonate were more toxic in mice than regular and coarse particles.

The Office Action does not respond to the argument that on p. 14 of the December 13, 2006 Response that "whether it is in fact possible to obtain such an enhancement of both rate and extent of absorption of a particular drug cannot be predicted." The Office Action does not respond to the argument that "if for example one micronized drug shows improved bioavailability, it does not naturally extend or be extrapolated to metaxalone." The Office Action does not refute that these arguments are supported by the cited excerpts from "Remington's Pharmaceutical Sciences" at pages 14-15 of the December 13, 2006 Response. The Office Action does not respond to the argument that the cited teachings indicate "that there is no correlation between reduced particle size and bioavailability in the unpredictable pharmaceutical arts" and similar recognition in the U.S. Manual of Patent Examining Procedure (MPEP) 2164.03.

The Office Action does not respond to the foregoing understanding of one of ordinary skill in the art. Instead, the Office Action takes a rigid approach by pointing to a teaching in Gilis of micronization for cisapride, and contending that it would have been obvious that a micronized form of metaxalone would have enhanced bioavailability on an empty stomach.

Even a cursory reading of Gilis demonstrates that this conclusion is not supportable. Of course, one fundamental problem with the rejection is that Gilis is directed towards a different drug -- cisapride, not metaxalone. The pharmaceutical arts are not predictable, and it is settled that it is improper to expect that the teachings of one reference in the pharmaceutical arts may be applied to another.

Even if it were possible to overlook this deficiency, the rejection would still not follow from a combination of Scaife with Gilis. Gilis starts out by referring to several prior art attempts to improve the bioavailability of cisapride (see generally col. 1-3). After reporting that these efforts were unsatisfactory, Gilis teaches to provide cisapride in one of several salt forms -- sulfuric, L-tartaric. D-tartaric, or citric (see col. 4, lines 7-15).

Gilis then teaches that "[i]n some cases it may be useful to use a coarser material (than the micronized or microfine material) of the presently described salts of cisapride." Col. 5, lines 51 *et seq.* This is because, when the material is too fine, "there may arise problems with producing tablets," and "the tablets show low assay values." *Id.* These teachings are in accord with the other references cited above that indicating that there is no correlation between reduced particle size and bioavailability in the unpredictable pharmaceutical arts. *Accord,* MPEP 2164.03, noting predictable factors, such as mechanical or electrical elements, and **unpredictable** factors, such as most chemical reactions and **physiological activity**.

Thus, the skilled artisan would be led by Gilis to conclude that it is very difficult to enhance the bioavailability of cisapride (as is evident from Gilis' description of the failed efforts of prior art workers in the field). The skilled artisan would then be led to conclude that particle size is not critical, and in fact that particles that are too small can have "problems" and "low assay values." Gilis purports to solve the bioavailability problem by providing a sulfate, tartrate, or citrate salt. The skilled artisan would find no metaxalone-related guidance whatsoever from these teachings. Gilis' teachings to this effect are specific to cisapride. Of course, beyond all of this, the skilled artisan would somehow have to get past the fact that Scaife teaches away from use of any other form of metaxalone besides the conventional form. There is simply no reasonable expectation of success provided in the teachings of Scaife and Gilis for a particular form of metaxalone when dosed on an empty stomach over that of the commercially available form Skelaxin®.

Gilis et al. discloses that, instead of using cisapride monohydrate, if solid oral dosage forms of certain cisapride salts like tartrate are used, the formulation can be taken independently from the meal. Gilis et al. relates to use of certain salt forms of cisapride like tartrate, sulfate and citrate. A person of ordinary skill in the art would know a "solubility-improved form of



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metaxalone" can not be a tartrate, sulfate or citrate salt of metaxalone because formation of such salts with metaxalone is not possible. Thus, Gilis et al. does not teach the preparation of a "solubility-improved form of metaxalone" in the form of a metaxalone salt. Also with reference to particle size modification to obtain a solubility-improved form of cisapride or by inference metaxalone and therefore enhanced bioavailability, the examples in Gilis et al. disclose cisapride tartrate formulations without mentioning the particle size. Example 14 on dissolution studies and Example 15 on bioavailability studies do not show the effect of particle size on bioavailability. These comparisons in Gilis et al. are made between the cisapride monohydrate and cisapride tartrate formulations, and there is no disclosure that enhanced oral bioavailability is attributable to any micronization.

The disclosure on particle size in Gilis et al. at Col. 5, starting on line 32, states that "tablets or capsules according to the invention comprise salt forms of cisapride, preferably cisapride(L)–tartrate which are preferable in microfine or micronized form for some uses." Emphasis added. Further, Col. 5, starting on line 51, Gilis et al. states that in some cases for instance, when direct compressing of tablets is desired, "it may be useful to use coarser material (than the micronized or microfine material) of the presently described salts of cisapride." Thus, Gilis et al. does not disclose only micronized particles of salts of cisapride but also discloses coarser particles of salt forms of cisapride. The disclosure in Gilis et al. about particle size is related to tabletting problems and not bioavailability problems. Also, col. 6 of Gilis et al. discloses that formulations of micronized material have 50 % of particles which may have diameter larger than 24 μm, and formulations of coarser material have 50 % of particles which may have diameter larger than 50 μm.

There is no guidance or teaching how to modify Scaife et al. with Gilis et al. to obtain the present invention. A person of ordinary skill in the art reading Gilis et al. would not have known whether to use micronized particles or coarser particles and use of particular particle size or know how to prepare any other solubility improved form of metaxalone to obtain a pharmaceutical composition of metaxalone having enhanced oral bioavailability. It is clear from above that Gilis et al. does not teach the preparation of a "pharmaceutically acceptable solubility-



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improved form of metaxalone" including reducing particle size of metaxalone to affect its bioavailability. Even if the Office was to cite another reference on a specific drug whose bioavailability was enhanced by reducing particle size, it would not be apparent or obvious to a person of skill in the art that the same would occur with metaxalone. Even if given such hypothetical prior art, there would be no reasonable expectation that metaxalone in a pharmaceutically acceptable solubility-improved form (e.g., micronized metaxalone) would have enhanced oral bioavailability, i.e., both increased rate as well as extent of absorption, as compared to the pharmaceutical composition of metaxalone corresponding to New Drug Application No. 13-217 when they are administered to a patient on an empty stomach.

The present case is analogous to *United States v. Adams*, 383 U.S. 39, 40 (1966), which was recently recited in *KSR v. Teleflex* – the analogy residing in the unexpected or unpredictable results in the present case and *Adams*. In *KSR*, the Court stated that "normal expected progressive innovation" is not an invention, but the present invention does not give something expected because the result as explained above is unpredictable. *KSR* therefore supports the patentability of the present invention particularly by reciting *Adams*.

Additionally, there is no motivation to combine the Gilis and Scaife references. The Office Action's position that citation of Gilis et al. in Scaife et al. is a motivation to combine the two is not correct and the Office Action does not provide support from case law in support of this position. The motivation should be derived from the prior art themselves or from the general knowledge of a person of skill in the art. Even if it is assumed that Examiner's position is correct, it is amply explained herein that obviousness does not flow from a combination of the cited references taken together with general knowledge of a person of skill in the art because they do not provide each and every feature of the invention.

Scaife et al. investigates effect of food on bioavailability of metaxalone and expressly teaches that bioavailability of metaxalone increases when administered with food. It would not be obvious to one of ordinary skill in the art to go in an opposite direction of Scaife et al.'s teachings and expect to achieve enhanced bioavailability in a pharmaceutically acceptable solubility-improved form as compared to the composition of Scaife et al. when they are administered to a patient on an empty stomach.



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The secondary reference Gilis et al. teaches a pharmaceutical composition comprising a certain salt form of cisapride for the treatment of a gastrointestinal disorder without a drug food interaction. As explained above, Gilis et al. in no way suggests that metaxalone in a pharmaceutical composition of present invention would lead to the unexpected result of enhanced bioavailability of metaxalone even when administered to a patient on an empty stomach.

A review of the prosecution history of the Scaife patent shows that Scaife filed a Petition to Make Special, and submitted the results of a "Preexamination Search." *See* Exhibit D. The record does not show exactly what the search parameters were, and how the Gilis and Cheng references were located using the key term "metaxalone" because neither of these references contain the word "metaxalone." Scaife did not identify Gilis as a reference "determined to be most closely related to the subject matter of the pending claims." See pp. 1-2 of Exhibit D. Scaife stated that Cheng discloses a controlled release antihyperglycemic tablet, and that "[t]here is no teaching or suggestion of Applicants' invention directed to increasing the oral bioavailability of metaxalone to a patient by administering it in a pharmaceutical composition with food." See p. 8 of Exhibit D. Similarly, there is no teaching or suggestion in Cheng of the present Applicant's invention. As previously noted, "[i]n formulating rejection under 35 U.S. C 103 (a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed."

Scaife et al. does not teach "A pharmaceutical composition comprising metaxalone in a pharmaceutically acceptable solubility-improved form and at least one pharmaceutically acceptable excipient, characterized in that the pharmaceutical composition has enhanced oral bioavailability as compared to the pharmaceutical composition of metaxalone described in New Drug Application No. 13-217 when they are administered to a patient on an empty stomach." Neither does Scaife et al. teach "A pharmaceutical composition comprising micronized metaxalone" as claimed in claim 3.



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As noted above, Scaife reports experimental results obtained with metaxalone that corresponds to New Drug Application No. 13-217. The way that Scaife seeks to improve the extent of absorption of metaxalone is to administer conventional metaxalone with food. Scaife says nothing about using a form of metaxalone that is different from that corresponding to NDA 13-217. Indeed, Scaife discloses that providing metaxalone with food is a satisfactory solution to his concerns with the extent of absorption. One skilled in the art would thereby be taught away from the notion of a form of metaxalone that is different from the conventional form.

The Office Action rejected applicant's explanation that reliance on Cheng et al. is not proper on the basis that Cheng et al. is cited by Scaife et al. The Office Action, however, presents no supporting case law for this position. In fact the first requirement is that the prior art must disclose at least one element of the claimed invention. Cheng et al. does not do that. Cheng et al. does not disclose any metaxalone composition with enhanced bioavailability or any method for enhancing bioavailability of metaxalone. Cheng et al. does not disclose any drug composition per se with enhanced bioavailability.

Please refer to Table 1 in column 9 of Cheng et al. The AUC values are only a fraction of the reference product, meaning that the bioavailability is actually decreased rather than enhanced. Example 1 in Table 1 has no absorption enhancer. Examples 2 and 3 of Table 1 have sodium lauryl sulphate as the absorption enhancer, however, in spite of that the ratio of AUC and therefore the bioavailability in comparison to AUC for Glucophage®, the reference product (Test/Reference ratio of AUC) was less than 1.

Because Scaife et al. and Gilis et al., or Scaife et al. and Cheng et al. singly or combined, do not teach or suggest each and every feature recited in the amended claims, the claimed invention is novel and non-obvious in view of the prior art. Accordingly, applicants respectfully request that the prior art rejections be withdrawn.



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Conclusion

In view of the foregoing, it is respectfully submitted that the pending claims are in condition for allowance. The Examiner is invited to contact the undersigned should it be deemed helpful to facilitate prosecution of the application.

Respectfully submitted,
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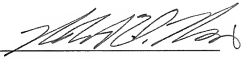
Date: July 2, 2007

By: 

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